Medical Isotope Research and <u>Production</u> Program (MIRP)

Collider Accelerator Department

Brookhaven National Laboratory

Suzanne V Smith

Production Manager

Overview

- 1. Production of Sr-82 and other radioisotopes
- 2. cGMP compliance
- 3. Improvements to BLIP and TPL Facilities
- 4. Radioisotope Production and Costs
- 5. Future Goals

MIRP - Production

To deliver excellence and innovation in the production of radioisotopes for the benefit of the national interest using high-energy protons at Brookhaven National Laboratory (BNL) for the Department of Energy Isotope Program.

To ensure world class training and development in the application of high energy protons for radioisotopes production for our next generation of radiochemists, nuclear chemists, chemical engineers, physicists.

Production of Sr-82 and other radioisotopes

Isotope Production and Distribution

- a) Supply **Sr-82 Active Pharmaceutical Ingredient (API)** in compliance with current Good Manufacturing Practices (**cGMP**).
- b) Supply radioisotopes such as Ni-63, Fe-55, Zn-65, and Rb-83.
- c) Support the Ac-225 National R & D irradiation effort (LANL, ORNL and BNL)

Maintain and Upgrade Radiochemistry Facilities to ensure we are responsive to the needs of the DOE Isotope Program

- a) Ensure facilities are fully operational.
- b) Support Raster Project as required.

MIRP Production Team Profile

Production (5.87 FTE)

- **0.91** scientific FTE,
- 2.97 professional FTE's,
- **1.96** technical FTE's.
- 1.0 profession P1 P3 (under recruitment)

Quality Assurance and Quality Control (2.58 FTE)

1.42 FTE Quality Assurance Senior Professional Specialist (J Odin-McCabe) plus Quality Control Professional Specialist (IG) - 2 Jun 2014.

1.16 FTE (0.6 FY15) Research Scientists (DM, JF)

BNL Support and C-AD - Draw on specialist expertise (1.0 FTE) from C-AD for thermal and mechanical analysis (using engineering code ANSYS) of target materials, design and construction of target assemblies, MCNPX for radioisotope yield and dosimetry calculations and infrastructure maintenance as well as Radiological Control Division for Health Physics Support.



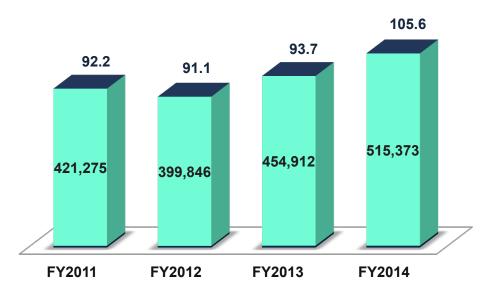


Fig. 1. Comparison of Integrated Current and Average Current.

- Overall increase (15.9%) in integrated current since FY12 to FY14 on target.
- Routine maintenance (FY14 every 2 to 3 weeks for 4 hours) schedule assisted to improve reliability at BLIP.

BLIP statistics

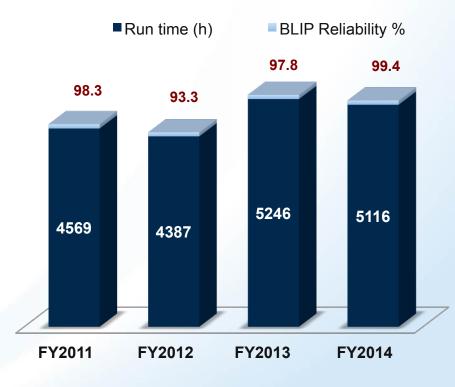
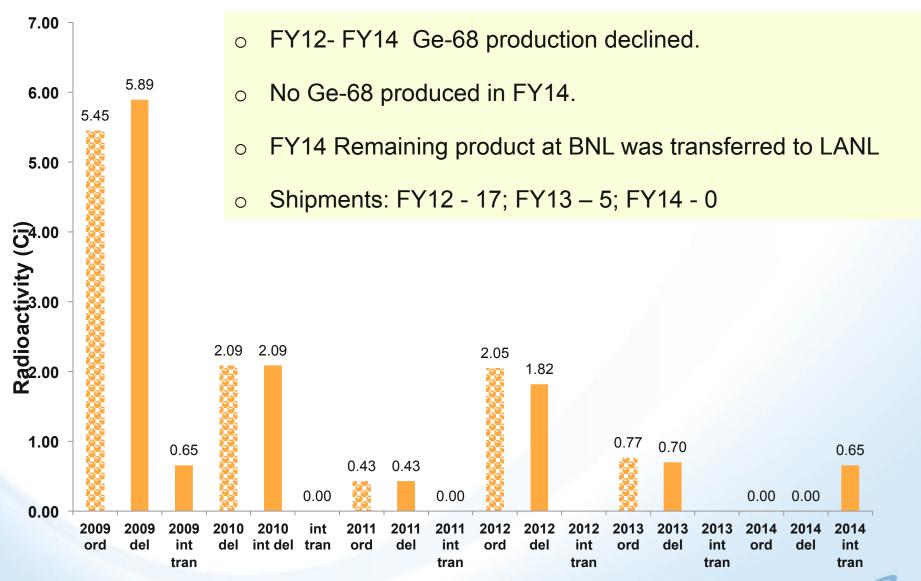
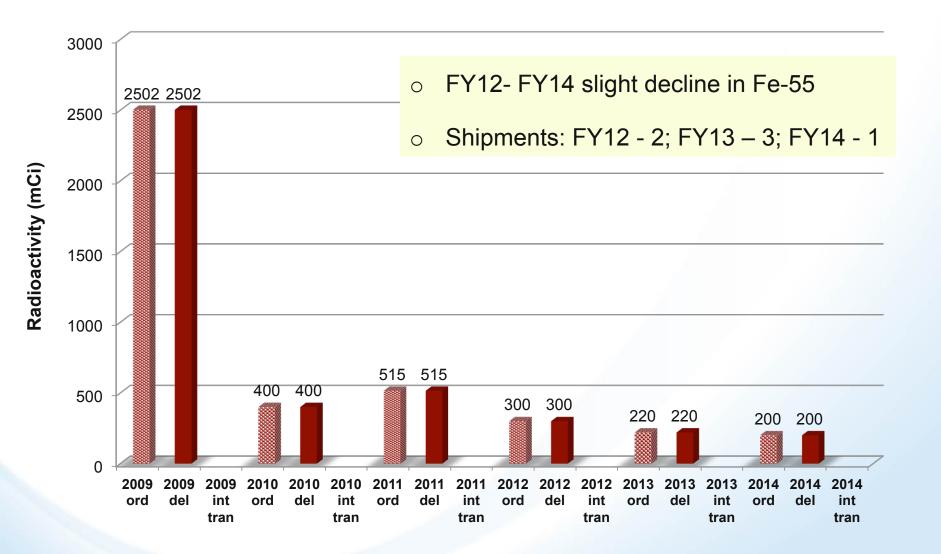


Fig. 2. Comparison of BLIP run time (h) and reliability

Delivered Qualified Ge-68 at Customer Calibration

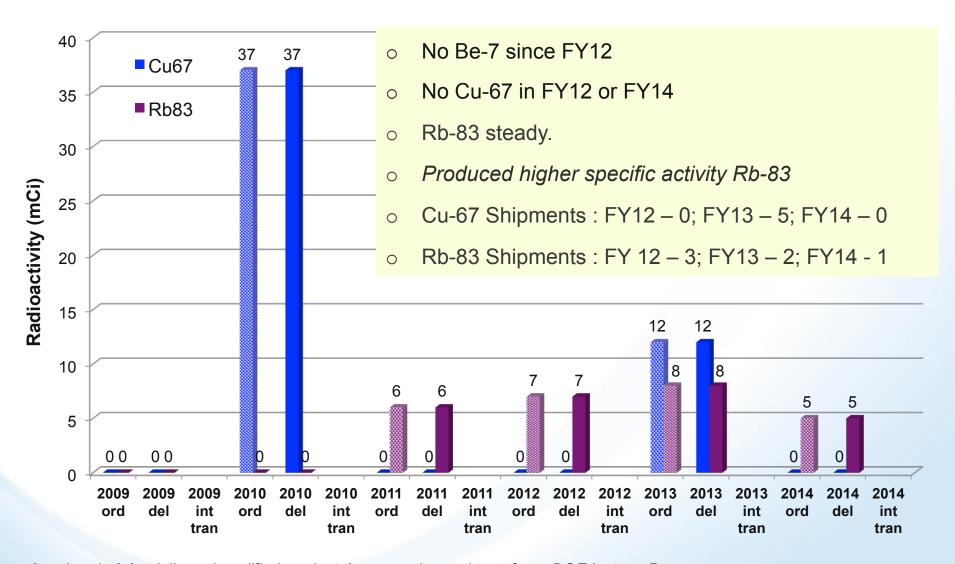


Delivered Qualified Fe-55 at Customer Calibration

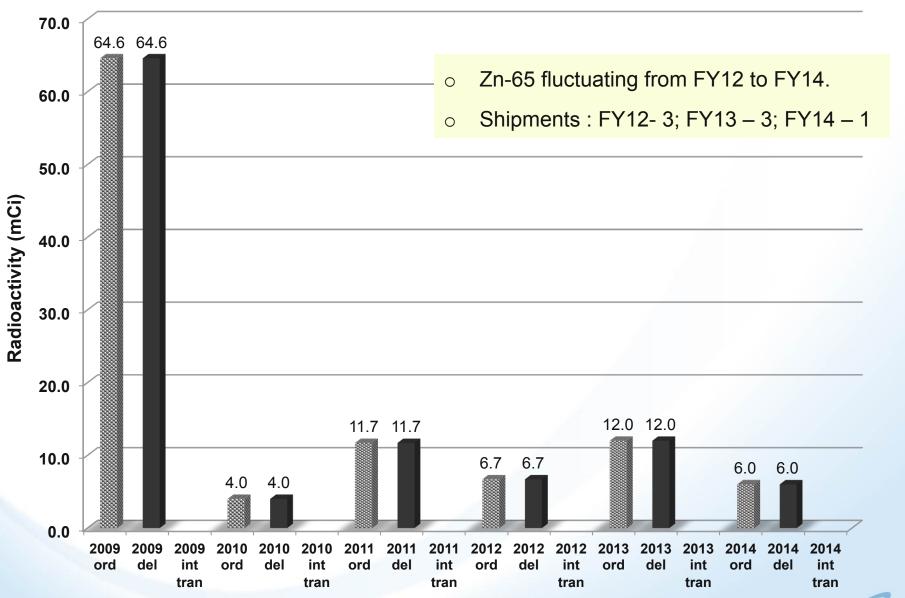




Delivered Qualified Cu-67 and Rb-83 to Customer

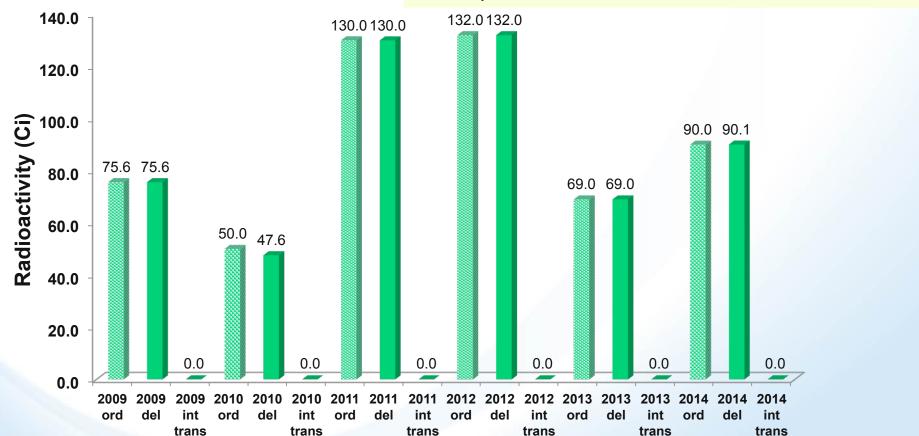


Delivered Qualified Zn-65 at Customer Calibration



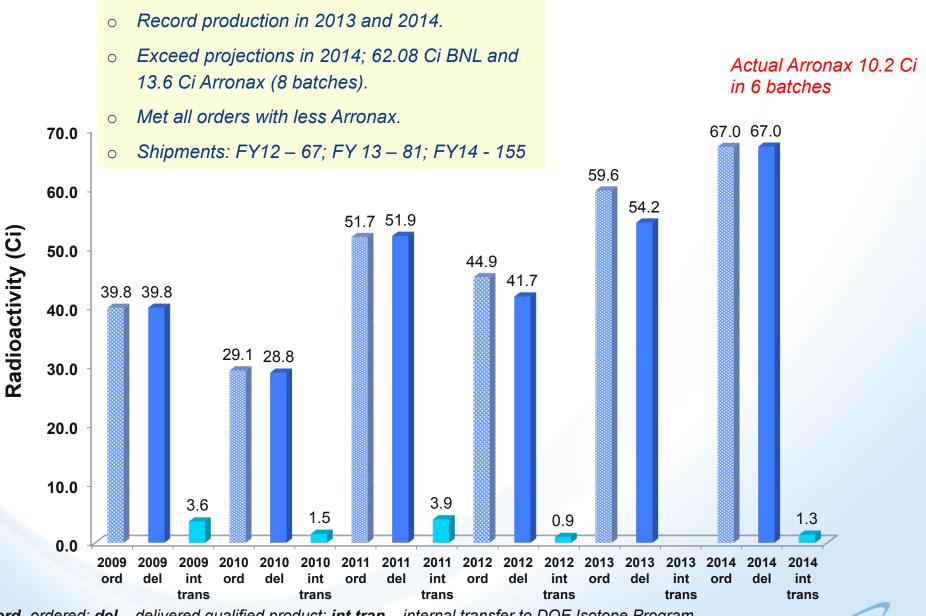
Delivered Qualified Ni-63 at Customer Calibration

- Ni-63 appears to fluctuate.
- Total deliveries for FY12 to FY14 slightly higher than previous review period.
- Shipments: FY12 10; FY13 6: FY14 9





Delivered Qualified Sr-82 at Customer Calibration



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Outcome External Audits 2013

DraxImage – 7 Major (3 repeats); 10 Minor; 10 Recommendations

Bracco – 6 Major (5 repeats) and 1 Minor

Opportunities for Improvement

- cGMP training
- Job Delegations
- Identify specialist / responsible persons
- Improve on documentation of processes
- Qualifying of materials
- Preparation of intermediates
- Identification of critical process parameters
- Identification of in-line process controls



Goals for the Production Program in FY14

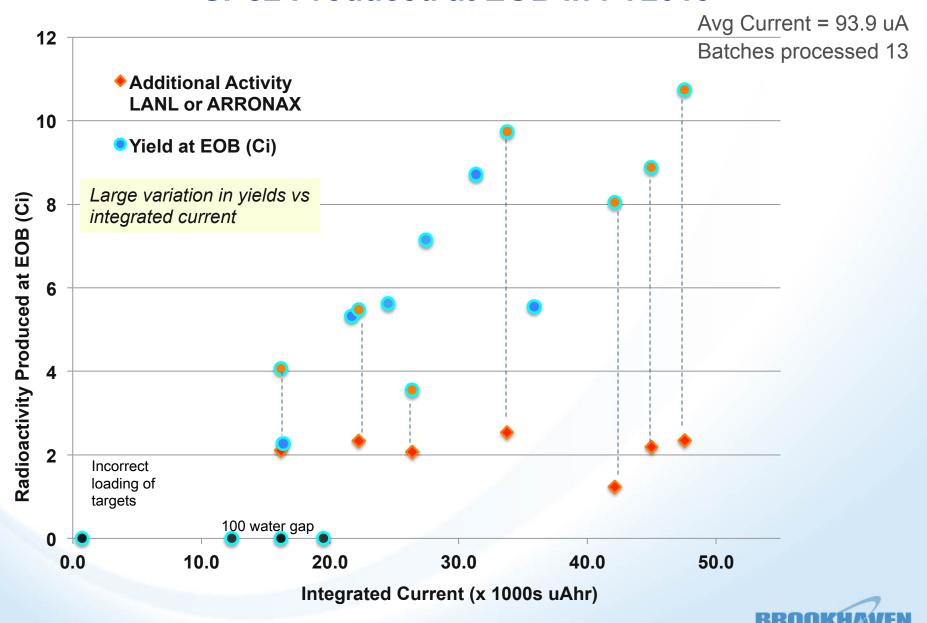
- 1. Improved overall
- a. safety,
- b. reliability,
- c. quality of products and
- d. cost effectiveness.
- 2. Implement processes that are compliant with cGMP for the production of Sr-82.
- 3. Develop staff in cGMP production of radioisotopes; *including technical* writing and design and implementation of validation protocols.
- 4. Upgrade the facility to ensure compliance with cGMP and efficient production of Sr-82 and other industrial and research radioisotopes.

Quality Systems and Processes Introduced in FY14

Compliance with cGMP

- Contracted trainer for cGMP- MIRP staff and C-AD management and support staff participated.
- Redefined Production, QC and QA roles and responsibilities.
- Established new Change Control Process.
- Defined target array procedures and safety review process for integrating research and cGMP production of Sr-82.

Sr-82 Produced at EOB in FY2013



Five Process to produce Sr-82 API

Name of Process	evaporations	columns	Days to complete (includes QC/QA)
Semi-Processed Arronax	5	3	5
BNL targets	4	3	5
Semi-processed Arronax or LANL and BNL targets	5	3	5
DOE blending	nil	nil	1
Reprocessing	3	1	2

Before start of season

- Revised qualifying of starting materials, preparation of intermediates and their analysis.
- Revised methods for each process.
- Removed rework options for processing and any hand process changes.

Monitored processes throughout the year to identify

- Critical process parameters (impact yield and quality of Sr-82 significantly)
- o In-line process controls (deviation may result in impact on quality of product)
- Impact of equipment (erognomics of equipment and ability to conduct task with precision week to week)
- Skill of staff (ability to execute operations repeatedly with high precision)
- Verification steps (essential to for independent assessment e.g. "soft dryness")

Monitored radiation dose in duct work of TPL, acid scrubber (upto 300 mR) and HEPA filter on roof.

Sr-82 Processes Completed in FY2014

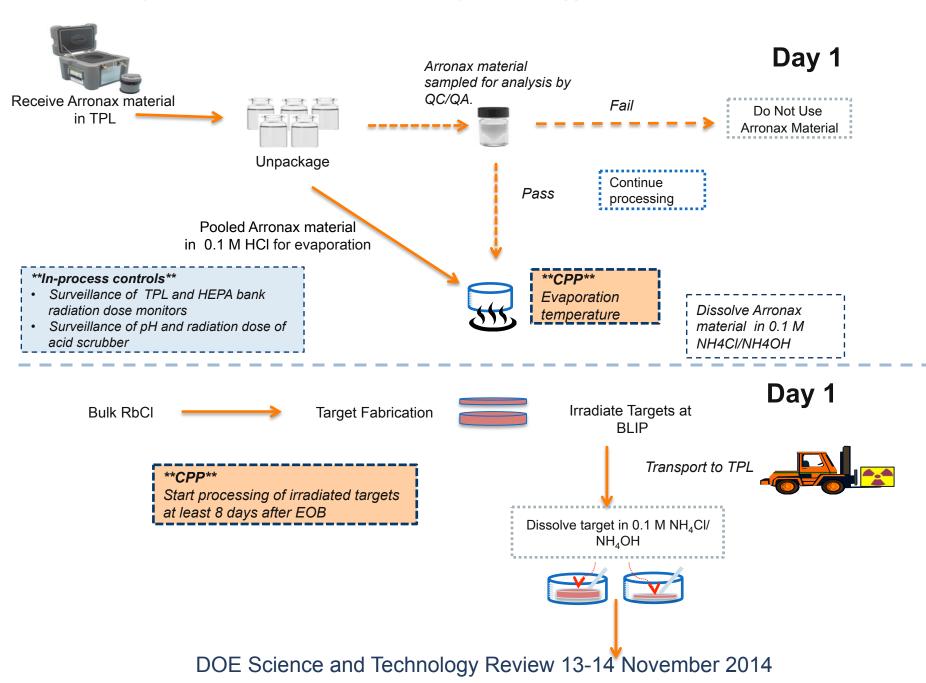
26 batches were prepared using the following processes

0	BNL Targets only	(11)
0	Semi-processed Arronax Targets Only	(4)
0	Semi-processed Arronax and BNL targets	(2)
0	Reprocesses out of specification Sr-82	(4)
0	Blended qualified Sr-82	(5)

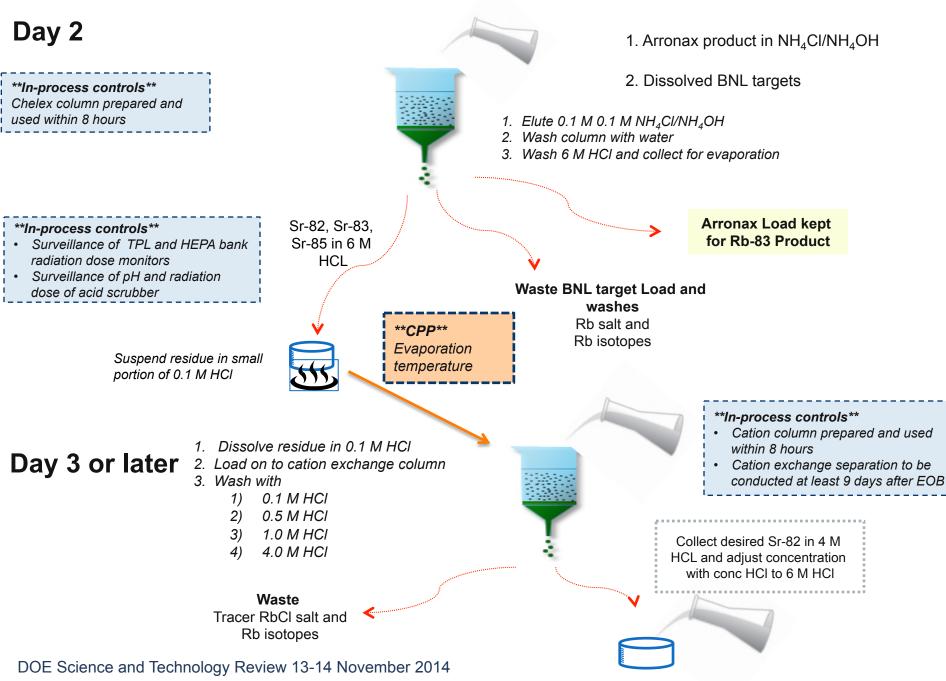
Validation Status

- BNL Targets only completed
- Semi-processed Arronax Targets only completed
- Blending D completed
- Semi-process Arronax and BNL targets to be completed in FY15
- Reprocessing completed.

Processing of Arronax and BNL target Part (I)

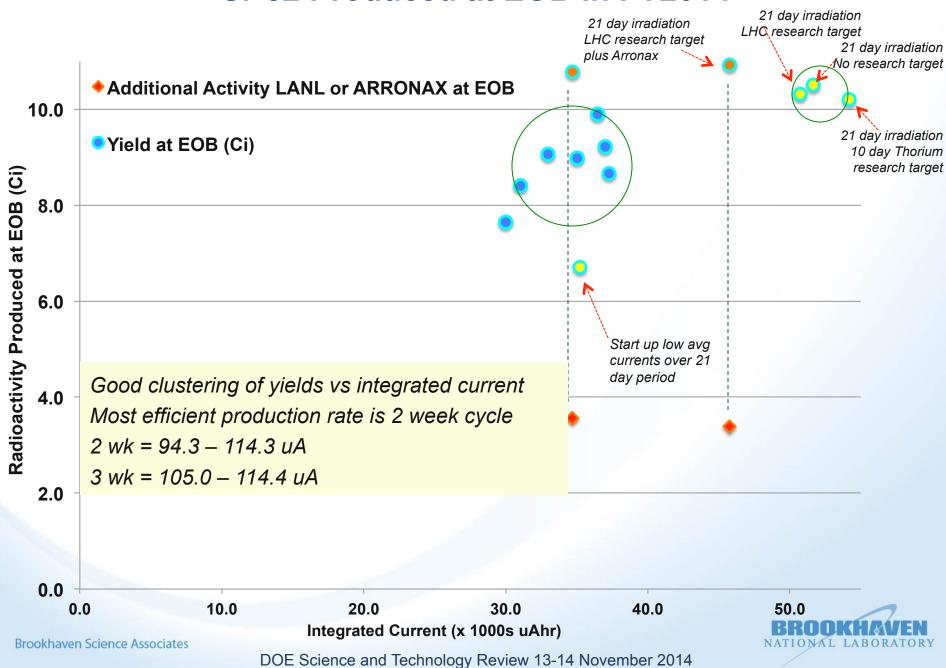


Processing of Arronax and BNL target Part (II)



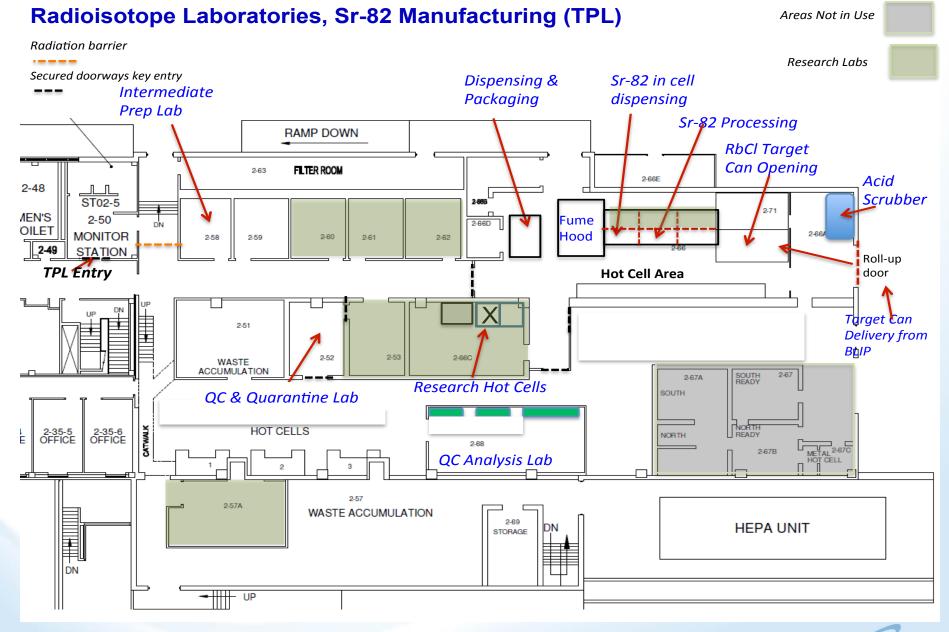
Processing of Arronax and BNL target Part (III) Load anion column with acidified Day 3 cation column product **In-process controls** 2. Wash 6 M HCl and collect for Anion column prepared and used evaporation within 8 hours **CPP** Add conc. HNO₃ to residue and Evaporation evaporate (remove organic temperatures compounds) **In-process controls** Surveillance of TPL and HEPA bank radiation dose monitors Surveillance of pH and radiation dose of acid Add 6M HCl to residue and evaporate scrubber (converts to SrCl₂ salt form) Independent visual verification that final evaporation is complete **CPP** Dissolve pure Sr-82 in 0.1 M HCl Day 4 Final bulk product Transfer to final product bottle sampled for analysis by QC/QA. Pass Blend remaining product Fail with DOE inventory. Final product Certificate of Reprocess release using an **Analysis** appropriate procedure Dispense Day 5 Package for shipment DOE Science and Technology Review 13-14 November 2014

Sr-82 Produced at EOB in FY2014



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Change infrastructure – *enhance productivity*

No.2 portal



Sr-82 dispensing cell

product.

Left Portal Access obstructed by balance/steel block for Sr-82 dispensing.



Second port easily accessed. Research samples can mover freely in and out of hot-cells

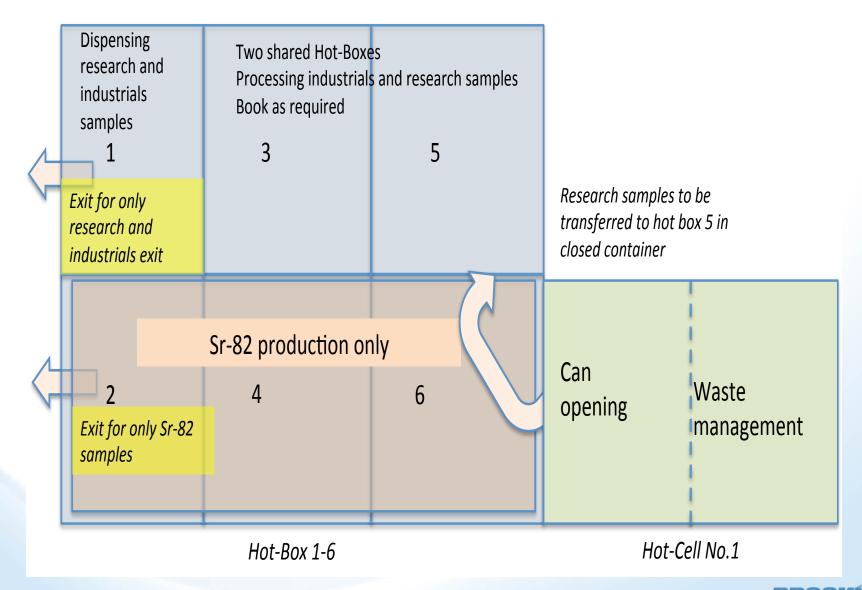
2. Resulted in **reduction** in radiation **dose** to staff, **waste** generated, **time** and **volume** of product required for QC analysis.

New process for analysis and sampling of

retention and quality control of Sr-82 final

3. Opening access to second port **reduced** potential for **cross contamination** of Sr-82 and free movement for Research samples and full function of 6 hot-cells.

Change infrastructure – *enhance productivity*



Development projects in FY14

Goal: To enhance compliance to cGMP, reduce dose to staff and improve on precision, efficiency of production and analysis of Sr-82 API.

Production Staff and Four Summer Student Interns evaluated the following.

- Critical Process Parameters established binding coefficients for radiometals and investigate optimization of Sr-82 production process.
- Development and validate of acid scrubber prototype for hot-cell.
- Development and validate of programmed logic controlled hot-plate (with CAD programmers).
- Develop methods for determining LLOQ for Rb-83 in presence of Sr-82 by gamma spectrometry.
- Development and validation of automated dispensing apparatus.



Safety – API and Contamination

- Current method for dispensing is demanding.
- Increase likely hood of contamination of work areas.







Safety - New approach to dispensing

- Used standard disposal syringes ranging from 1.0 to 100 mL.
- Precision and accuracy excellent.
- Software controlled.
- Reduce dose
- Reduce contamination of API
 - Reduce contamination of work areas.

TPL infrastructure Improvements and Maintenance FY14 and FY13

FY14

- Annual contracted repair of hot-cell master slave manipulators.
- Established laboratory for preparation of Starting and Intermediate materials and Quality Control of SM and IM and quarantine protocols.
- Relocated Ni-63 processing from Sr-82 dispensing hot-cell to research hotcell.
- Relocated Radiation Monitors for HEPA filter bank in TPL processing lab.
- New maintenance and operation for Acid scrubber (pH electrode not working).
- Descaled distilled water system for Bld 801 radiochemistry laboratories.

TPL infrastructure Improvements and Maintenance FY14 and FY13

FY14

- Replaced "end of life" two variable speed motors for ventilation fans for TPL Hot-cell.
- Repaired ventilation monitoring panel for Hot-cells and establishing baselines.
- Replaced HEPA filters and pre-filters for semi-hot-cell fume-hoods.
- Installed blast gates in room 57A hoods 1 and 2.

FY13

Redesigned and fabricated new target can opener.

BLIP infrastructure Improvements and Maintenance FY14 and FY13

FY14

- Replaced old (40yrs) with a 15 tonne chiller system (which has sufficient cooling capacity for BLIP to run at 200 MeV and 115 uA and future BLIP upgrade).
- Sand shielding beneath BLIP hot-cell complete
- Installed additional shielding on front of BLIP hot-cells
- Installation of radiation hardened cameras in BLIP hot-cells.
- Installed new fire alarm panel to align with code.
- Installed upgraded security system (included card reader and cameras)
- Annual contracted repair of hot-cell master slave manipulators

BLIP infrastructure Improvements and Maintenance FY14 and FY13

FY14

- Replaced 3 faulty primary water flow meters.
- Redesigned target box door to ensure locking of box. (lid opened due to corrosion, wear and tear)

FY13

- Installed metal guards preventing access to high radiation areas (Prevents accidental radiation exposure).
- Replaced plastic encasement around target box assembly. (to cuts down on stack emissions).
- Replaced HEPA and roughing filter in ventilation system. (It has a 10 year life span.)

Safety – Reduction in dose to staff

- BLIP staff dose reduced due to change in loading practices (no target failures) and sand shielding (8R to 30 mR).
- Additional shielding on front of BLIP hot-cell further contributed to reduction. Real impact will not be realized until FY 15
- TPL staff dose reduced from changes to evaporation process and QC analysis (background in TPL reduced).
- QC staff no increase in dose to QC staff now preparing own samples.

Challenge forward

Packing and Shipping

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Mission Ready and Production Costs FY14 and FY13

2014	Inf – BLIP (\$)	Inf – HC (\$)	Production (\$)		Rational variance	
Salary	236482	1183013	990732	X	Staff for Sr-82 production	
Recharges	47686	186898	61704	✓		
Purchases & Subcontracts	121268	395888	256411	✓		
ODC (Other Direct Charges)	307035	449797	434954	X	HP support maintenance Biodex shipments	
Research Machines			2303173	X	Dedicated beam time	
Power		31164		✓		
Space	72551	434161		✓		
Waste	30656	141179	138387	1		
Total Costs	815678	2822100	4185361			
2013	Inf – BLIP (\$)	Inf – HC (\$)	Production (\$)	A		
Salary	419167	1307418	680464	Х		
Recharges	21103	170888	117747	1		
Purchases & Subcontracts	81739	511772	236795	1		
ODC	135202	687783	134315	X		
Research Machines	114		1477946	X		
Power		23048				
Space	73162	414881				
Waste		211163	147117	1		
Total Costs	730487	3326953	2794384			

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Moving forward – FY 15 - FY16 targets

- Validation of last production process will be completed.
- Analytical methods and qualify of instrumentations should be completed before end of production season.
- Using new information from distribution coefficient studies optimize separation process for Sr-82.
- Upgrade Gamma Spectrometry Instrumentation.
- Install plastic curtain barriers.
- Establish baseline for Air Quality.
- Annual contracted repair for hot-cell master slave manipulators.

Moving forward – FY 15 - FY16 targets

- Developed marc II in-cell acid scrubber as first line of containment for radioactive volatiles.
- Changed the input lines for solutions to hot-cell.
- Implement PLC controlled hot-plates.
- o Implement lead shielding for dispensing apparatus in fume-hood.
- Radiation monitoring system for BLIP tank cooling water.
- Set up quality assurance method for BLIP beam
 - Foil irradiations, digestions and phosphor imager.
- Install upgraded HEPA and Pre filters for hoods 1 and 2 room 57A.
- Design and fabricate new tray for horizontal transfer cask.

Moving forward – FY 16 targets

- Upgrades of beam and Ac-225 project will increase radiation dose to staff, particularly in dispensing and package.
- Strategic plan for infrastructure upgrade needs to be implemented to prepare for impact of upgrades and growing R and D portfolio.

Q and A



Additional Questions and Answers

What is the variation on radioactivity for Arronax Batches?

Batch ID	Arronax reported (mCi)	BNL assayed (mCi)	%difference=(BNL-Arr)/Arr
Sr82-A-14-01	1970.02	1952	-0.91%
Sr82-A-14-02	2542.02	2413.6	-5.05%
Sr82-A-14-03	2567.7	2461	-4.16%
Sr82-BA-14-01	2556.1	2515	-1.61%
Sr82-BA-14-02	2593.77	2401	-7.43%
Sr82-A-14-04	2694.1	2667.7	-0.98%



Mission Ready and Production Costs FY14 and FY13

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Budgets for 2014 and 2013 Actual vs Requested Budget

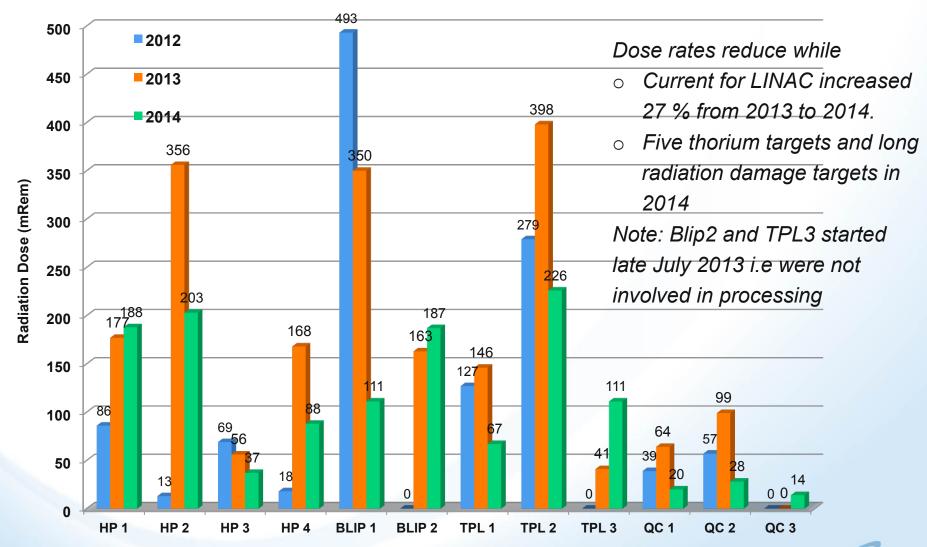
	FY2014		FY2013	
	Actual	Budget	Actual	Budget
Infrastructure-Hot Cell	2,822,100	3,288,655	3,326,953	3,032,621
Irradiation Infrastructure	815,678	808,960	730,487	730,604
ProductionSr-82	4,107,698	4,508,667	2,356,396	1,728,108
ProductionZn-65	24,634	24,155	9,238	12,578
Production Ge-68	512	310,588	259,213	402,972
Production - Y-86	0	23,425	45,932	14,132
Production Fe-55	1,246	5,965	1,564	3,637
Production Cu-67	12,190	86,431	101,746	48,741
Production Be-7	0	15,802	0	10,113
Production NI-63	20,171	27,005	15,928	13,295
Production Fe-52	0	12,329	0	
Production Rb-83	18,910	17,154	4,366	7,969
65356/65356 ARRA-Dvlp Spprt Isotp Prod	207		188,984	
ARRA-Dev PET Isotope Yttrium-86	0		(162)	
ARRA-Study of Zinc Rctn Cu-67	0		2,447	
00614 Isotope Research & Development Core	595,446	273,378	417,601	
00599 Prod of High Specific Activity Cu As	112,435	352,833	30,943	
00597/00597 Development of Ac-225	204,845	424,318		
70046 AIP Raster Upgrade	1,645,906			
70056 Linac Intensity Upgrade Ph 1	60,238			
	10,442,215	10,179,665	7,491,636	6,004,770

Budget for 2013 and 2014 Budget and Funding Guidance and Carryover

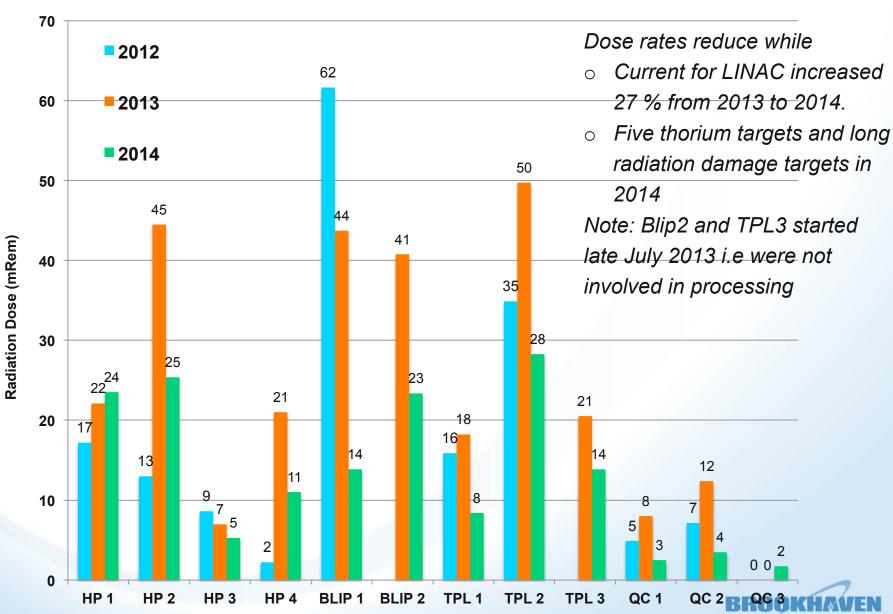
	FY2014 (budget)		FY2013 (budget)	
	Inf - BLIP	Inf - HC	Inf - BLIP	Inf - HC
Salary & ODL	377,398	1,332,831	343,155	1,330,263
Recharges	24,463	158,262	52,966	133,931
Purchases & Subcontracts	194,139	476,076	119,262	410,586
ODC	140,111	721,333	142,751	574,966
Research Machines				
Power		30,000		30,000
Space	72,850	419,904	72,470	417,716
Waste		150,249		135,159
Total Costs	808,961	3,288,655	730,604	3,032,621
Funding Guidance	536,000	3,085,000	520,000	2,900,000
PY Carryover	410,669	339,346	576,156	515,785

What is the radiation dose for staff in MIRP?

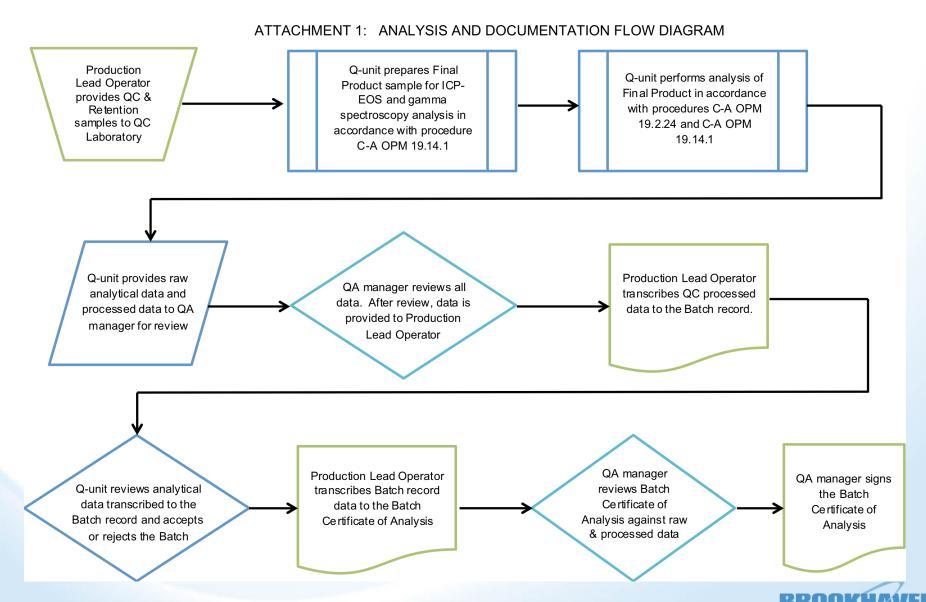
Year to Date Radiation Dose (Jan to Aug) for MIRP staff



Monthly Radiation Dose for MIRP staff (for Jan to Aug)



Do you have a decision tree for pass and failing products?



Revised in draft – based on draximage recent audit

ATTACHMENT 1: ANALYSIS AND DOCUMENTATION FLOW DIAGRAM

